

## REMARKS

Reconsideration of claims 1, 6-11, 20, 22, 25-28, and 47 is respectfully requested. Claims 26 and 27 are amended consistent with the language of page 8, 4<sup>th</sup> and 6<sup>th</sup> paragraphs, respectively.

The rejection of claims 1, 6-11, 25-28 and 47 under 35 USC 103(a) as unpatentable over Singh et al. (US 2003/0232089) in view of Olejnik (US 5597559) and Gohzu et al. (US 5013445) is respectfully traversed. The examiner relies on at least the two reasons below to reject the claims under 103(a).

“[I]t would be obvious to one of ordinary skill in that [*sic*, the art] to substitute the disclosed “gum” compounds, such as hyaluronic acid for Scleroglucan in the working example ID 21.

With regard to the viscosity ... and shear-viscosities, [in reference to claims 26 and 27] these appear to be conventional in the art, such that their determination would have been obvious to one of ordinary skill in the art using no more than routine experimentation.”

Official Action, page 4.

The examiner’s proposed combination is purely conclusory, and the rejection fails to explain why one of ordinary skill would look to the cited art, and in particular, to the two secondary references, to cure the stated deficiencies in Singh. The rejection fails to provide an evidentiary basis, or a finding of fact, to support the above statements. For example, following a careful review of the art in its entirety, why would one of ordinary skill substitute hyaluronic acid for scleroglucan in Singh’s ID21 as proposed? Greater evidence is required, and not simply that either is considered a biopolymer or is referred to in the art as a viscosity modifier.

Applicants respectfully submit that a proper rejection under section 103 requires more than just locating an element of a claim, and without more, combining that identified element with other claim elements identified in one or more references. This is true even following the holding in *KSR International*. The holding in *KSR International* does not stand for the proposition that the identification of known elements in one or more references without more is sufficient reason for proposing the combination of those elements. Mere identification of known elements in references is not the test for obviousness under section 103. This is particularly true in the context of a chemical invention. For the reasons that follow, Applicants

respectfully disagree with the examiner's legal conclusion, and submit that the examiner has failed to present a *prima facie* case of obviousness.

Singh describes an ophthalmic composition that includes a pharmacologically active agent and a mixture of at least two gum polymers. The mixture of the gum polymers is said to increase the retention time of the active agent in the eye. See, Abstract. As Singh describes, a major problem with the administration of ophthalmic drugs is the "rapid and extensive precorneal loss caused by drainage and high tear fluid turnover." In other words, how can one of ordinary skill develop an ophthalmic formulation that allows the active agent to remain in the eye for a time sufficient to therapeutically treat a particular ocular condition? We are all familiar with placing an eye drop in the eye and experiencing the wash out affect caused by an immediate tear flow response.

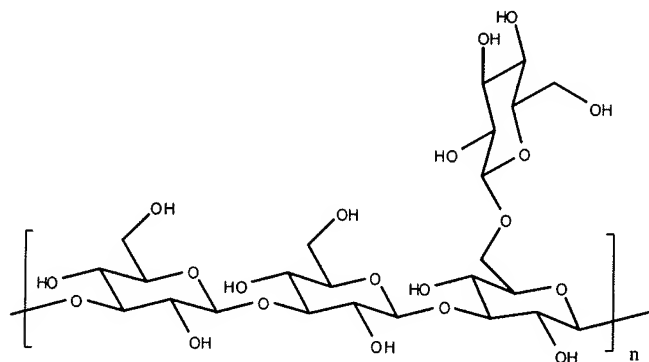
To address this problem, those in the art looked to increase the viscosity of the formulations hoping that the more viscous the formulation, the more difficult it would be to wash out. Singh describes the use of various combinations of gelling agents including gums. See, paragraphs [0008] to [0010]. Singh looked to improve upon the use of gelling agents to provide more effective ophthalmic formulations by testing various combinations. In fact, Singh lists five (5) synthetic gums, sixteen (16) natural polysaccharide gums and two (2) derivatized natural polysaccharides for a total of twenty-three (23) different gums. See, paragraph [0025]. Singh also refers to the optional addition of an "ophthalmically acceptable mucoadhesive polymer" in which hydroxypropylmethyl cellulose (HPMC) is one of ten (10) listed.

Upon a closer review, Singh directs one of ordinary skill to use a combination of gums to produce "unexpected advantages over individual gums". Paragraphs [0041] and [0044-53]. To optimize these unexpected advantages one of skill is directed to use a nonionic gum in combination with an anionic gum. For example, scleroglucan is listed as a neutral gum and hyaluronic acid is listed as an anionic gum. Given this more careful reading of Singh one of ordinary skill would rather add hyaluronic acid to ID21 rather than substitute the hyaluronic acid for the scleroglucan as proposed. Moreover, Singh's anionic gum of choice is propylene glycol alginate or alginic acid, not hyaluronic acid. In fact, six of the ten preferred gum combinations include propylene glycol alginate or alginic acid. See, Paragraphs [0044-53]. Therefore, one of ordinary skill having read Singh in its entirety would very likely choose alginic acid or one of its

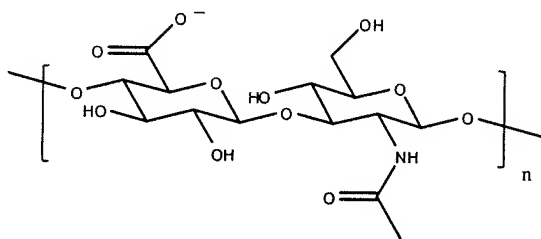
derivatives to combine with scleroglucan, and not as examiner proposes to substitute hyaluronic acid for scleroglucan.

Before we discuss the two cited secondary references, let us first look to the examiner's proposed substitution of the claimed hyaluronic acid for the scleroglucan, the latter of which is identified with HPMC in Example ID 21.

Scleroglucan is a nonionic branched homopolysaccharide that gives only D-glucose upon complete hydrolysis, and every third unit bears a branched  $\beta$ -D-glucopyranosyl unit. Scleroglucan is produced by fungi, and is not found in mammalian tissues. The chemical structure of scleroglucan is provided below.



Hyaluronic acid is an anionic glycosaminoglycan, and is best described as a polymer disaccharide composed of D-glucuronic acid and D-N-acetylglucosamine. Hyaluronic acid is found throughout mammalian connective, epithelial and neural tissues. For example, hyaluronic acid is a major component of synovial "joint" fluid. The chemical structure of hyaluronic acid is also provided below.



In spite of the differences in both chemical structure and biological function of these two natural compounds, the examiner, without reliance on any scientific or technical evidence, proposes that one of ordinary skill in the art would find it obvious to substitute hyaluronic acid for scleroglucan in Singh's Example ID 21 given the direction of the art, and in particular Singh,

as a whole. Applicant respectfully disagrees with the examiner's legal conclusion and submits that on this point alone the examiner's assertion of a *prima facie* case of obviousness falls.

Furthermore, the secondary references do not provide one of ordinary skill with any additional guidance over Singh alone. Singh describes the optional addition of an osmolality agent including the typical metal and organic salts as well as sugars including mannitol. A total of about twelve agents are listed only one of which is a hexahydric alcohol. Paragraph [0093]. Singh also refers to the optional addition of a buffering agent in which tris[hydroxymethyl]aminomethane (TRIS) is one of thirteen (13) buffer components listed. Paragraph [0094].

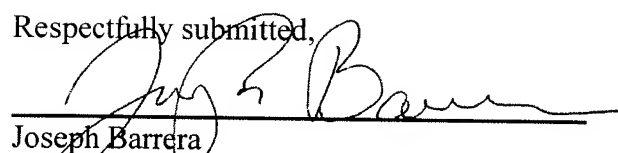
Yet in spite of the fact that each of the four recited components of claim 1 can be identified in Singh alone, that alone does not render the Applicant's composition obvious under §103 if one were to follow a Graham inquiry as mandated by the *KSR* Court. Much more than picking and choosing is needed. The possible combinations given the (23) different gums, the (10) mucoadhesive polymers, the (12) osmolality agents and the (13) different buffer components are in the thousands.

Why would one of ordinary skill select each of the recited four components from each generic listing described in Singh, or from the generic listings described in each of the secondary references? Mere identification and the piece meal, hindsight reconstruction of Applicants' composition is not sufficient. One of ordinary skill, either through the teachings of the art or by the common knowledge of one in the art, must be guided to the compositions claimed. Applicants compositions are quite specific, but more importantly, each of the recited components of the compositions must be viewed as a piece of a whole, not separately.

The proper §103 inquiry requires consideration of the invention as a whole. Neither Singh, nor any combination of references cited by the examiner, provide the necessary guidance to support a rejection under §103(a). The only explanation for the examiner's proposal, and hence rejection, is based on the hindsight reconstruction of Applicants own invention and the use of the application as a guide to make such selections. The Court, however, has repeatedly rejected that mental process as a means by which a proper case of *prima facie* obviousness can be established. Accordingly, Applicants respectfully request that the rejection as to the amended claims be withdrawn.

Reconsideration of this application is respectfully requested for the reasons stated.

Respectfully submitted,



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